REMARKS / ARGUMENTS

In response to the Office Action of April 22, 2009, Applicants have amended claim 1, which when considered with the following remarks, is deemed to place the present application in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

The inventors' declaration filed on September 13, 2005 has been objected to as allegedly defective. According to the Examiner, the document is defective because it allegedly contains handwritten changes to each inventor's residence that have not been initialed or dated by the individual who executed the declaration. The Examiner has therefore requested a new oath or declaration in compliance with 37 C.F.R. 1.67(a) identifying this application by serial number and filing date.

After comparing a copy of the duly submitted declaration in Applicants' file with the document that appears on PAIR, it appears that several handwritten markings must have been introduced by USPTO personnel. Specifically, it appears that the two letter country code "SE" and an "X" were handwritten by USPTO personnel next to "Sweden." Submitted herewith is an exact copy of the declaration that was submitted on September 13, 2005. Since the handwritten marks were added to the document after submission of the same to the USPTO, the objection should be withdrawn.

Claims 1-2 and 4-7 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The same claims have been rejected as allegedly indefinite under 35 U.S.C. § 112, second paragraph. In response to both rejections, claim 1 has been amended to recite: "A method of treating uveal melanoma said method comprising administering to a mammal in need of such a treatment, a therapeutically effective dose of 4-(4-methyl piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl) pyrimidin-2-ylamino) phenyl]-benzamide or a pharmaceutically acceptable salt thereof." Withdrawal of the rejection of clams 1-2 and 4-7 under both statutory sections is therefore respectfully requested.

Claims 1, 2 and 4-7 remain rejected under 35 USC §103(a) as allegedly obvious over Zimmermann et al (WO 99/03854) in light of Mouriaux et al ("Implication of Stem Cell Factor in the Proliferation of Choroidal Melanocytes", *Exp. Eye Res.*, 2001; 73:151-157) in view of Ijland et al. ("Expression of Angiogenic and Immunosuppressive Factors by Uveal Melanoma Cell Lines", *Melanoma Research*, 1999; 9:445-450). Zimmermann et al. has been cited for allegedly disclosing the beta-crystal form of the methanesulfonic acid addition salt of 4-(4-methyl piperazin-1-ylmethyl)-N-[N-methyl-3-(4-pyridin-3-yl) pyrimidin-2-ylamino)phenyl]-benzamide as useful for the treatment of warm-blooded animals suffering from tumor diseases, wherein a

quantity of the beta-crystal form of the methanesulfonic acid addition salt of the compound effective against the disease concerned is administered to the warm-blooded animal in need of such treatment. In addition, Zimmerman et al. has been cited for allegedly disclosing the active compound as an effective inhibitor of the angiogenic effect of VEGF. *See* page 7 of the office action.

Mouriaux et al is relied on for allegedly showing that activation of c-kit by its ligand was known to contribute to the proliferation of choroidal melanocytes, which are the cells involved in the pathogenesis of malignant melanoma of the eye, and therefore, one of skill in the art allegedly would have reasonably expected that uveal melanoma cells would express c-kit. *See* page 8 of the office action.

Ijland et al. has been cited for disclosing that uveal melanoma cell lines demonstrated significant VEGF secretion. *See* page 8 of the office action.

According to the Examiner, a person of skill in the art seeking treatment of uveal melanoma would be motivated to combine the teachings of Zimmermann et al. and Ijland et al. and thus arrive at the present invention. As stated on page 8 of the office action, the asserted obviousness of using 4-(4-methyl piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl) pyrimidin-2-ylamino) phenyl]-benzamide for the treatment of uveal melanoma is based upon the alleged fact that "(1) Zimmerman clearly discloses the active compound as an effective inhibitor of the angiogenic effect of VEGF and (2) Ijland et al. clearly discloses that six different human primary uveal melanoma cell lines (92-1, Mel-2-2, OCM-1, OCM-3, OCM-8 and EOM-3) each demonstrated significant VEGF secretion, which was indicative of angiogenic potency and vessel proliferation for neovascularization ..." April 22, 2009 office action, paragraph bridging pages 8-9.

Applicants respectfully traverse the rejection for the following reasons. Zimmermann teaches a specific crystal salt form of the active ingredient 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin- 2-ylamino)phenyl]benzamide, which - according to the opinion of Zimmermann - otherwise had been known as an anti-tumour agent. Said crystal form may under certain conditions be found in the methanesulfonate salt of this compound, and "has very advantageous properties". Thus, the disclosure of Zimmermann is clearly *limited* to the use of the crystal form (see section "Background of the invention"). Said crystal form can be used to treat a broad range of proliferative, and preferably (but not at all exclusively) tumorous diseases, as described on page 17, 1st paragraph of Zimmermann. Zimmermann does not mention uveal melanoma.

The treatment on page 16 of Zimmermann et al. relates to angiogenesis after transplantation of a foreign material into a mouse. Furthermore, the compound is active on inhibiting an externally added VEGF.

Thus, in summary, Zimmermann et al. is not limited to an anti-angiogenic effect of the crystal form in cancer, but generally teaches a broad anti-angiogenic effect in several proliferative diseases.

It is respectfully submitted that although Ijland et al. disclose that some uveal melanoma cell lines secrete sIL-1ra, IL-6, IL-8, IL-10, TGFβ and VEGF, the excretion of VEGF is not specific to uveal melanoma cell lines, but is common to many tumorous and proliferative diseases that require neovascularization. As an example, the reference of Creamer et al. (submitted herewith as Exhibit A) discloses that forms of psoriasis have microvascular hyperpermeability because of the excretion of VEGF. Furthermore, Shinkaruk et al. (submitted herewith as Exhibit B) discloses that VEGF is found in several types of tumors. Examples for these are, for example, ovarian, breast, and pancreatic cancers.

Nevertheless, this does not mean that an inhibitor of VEGF can generally effectively treat cancer cell lines excreting VEGF. The present application shows that compound I is ineffective in the treatment of skin melanoma cells (epithelial cells), which appear to be closely related to other melanomas. *See* page 6 of the specification, under "B. IC_{50} of Salt I on survival of 4 uveal melanoma cell lines (OCM-1, OCM-3, UM 92-1, mel 202 and skin melanoma cell lines (BE and DFB)."

Thus, the excretion of VEGF by uveal melanoma cell lines does not motivate the person of skill, starting from the generic anti-angiogenic effect of the crystal form taught by Zimmermann et al., to seek to use the compound of the invention specifically for the treatment of uveal melanoma cell lines, because uveal melanoma cells secrete VEGF. Many other cancer cell lines also secrete VEGF as described in the references provided at Exhibits A and B. Indeed, the present application teaches that the presently claimed compound was ineffective in treating skin melanoma cells, which cells are also known to secrete VEGF. Accordingly, withdrawal of the rejection of claims 1-2 and 4-7 under 35 U.S.C. §103(a) is therefore warranted.

In view of the foregoing, it is firmly believed that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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Mediation of systemic vascular hyperpermeability in severe psoriasis by circulating vascular endothelial growth factor.

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BACKGROUND: Severe forms of psoriasis can be complicated by systemic microvascular hyperpermeability. Vascular endothelial growth factor (VEGF) possesses potent vascular permeability activity. We suggest that VEGF enters the systemic circulation and acts on microvessels to mediate hyperpermeability. OBJECTIVES: To quantify renal microvascular permeability and circulating VEGF concentration in severe psoriasis, and to investigate the relationship between plasma VEGF concentration and skin and joint involvement. DESIGN: Inception cohort studies of patients with generalized pustular psoriasis and plaque psoriasis. SETTING: St John's Institute of Dermatology, London, England. PATIENTS: Twenty-two patients (15 men and 7 women) with moderate and severe psoriasis were recruited (age range, 29-77 years; mean age, 47 years); 5 had generalized pustular psoriasis, 2 had erythrodermic psoriasis, and 15 had moderate-severe plaque psoriasis. An age- and sex-matched control group of 17 individuals (10 men and 7 women) was recruited (age range, 29-69 years; mean age, 42 years). RESULTS: There was pathological proteinuria in patients with relapsing generalized pustular psoriasis, (4-fold increase in urinary protein excretion rate in relapse compared with remission). In patients with moderate and severe psoriasis, mean plasma VEGF concentration during relapse was approximately 2.5 times greater than during remission (mean VEGF(relapse) = 257 pg/mL; mean VEGF(remission) = 103 pg/mL; P<.01). There was a correlation between extent of skin involvement and plasma VEGF level (mean VEGF(severe psoriasis) = 365 pg/mL; mean VEGF(moderate psoriasis) = 149 pg/mL; P =.03). There was a correlation between presence of psoriatic arthritis and plasma VEGF level (mean relapse VEGF(arthritis) = 277 pg/mL; mean relapse VEGF(nonarthritis) = 103.5 pg/mL; P =.03). CONCLUSIONS: Generalized pustular psoriasis is accompanied by pathological proteinuria and elevated plasma VEGF levels. Plasma VEGF concentration is significantly elevated in patients with extensive skin and joint involvement and may act on renal microvasculature to induce hyperpermeability.

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Vascular endothelial cell growth factor (VEGF), an emerging target for cancer chemotherapy.

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Angiogenesis is a process of development and of growth of new capillary blood vessels from pre-existing vessels. When pathological, it contributes to the development of numerous types of tumors, and the formation of metastases. In order to grow, carcinoma need new blood vessels to form so that they can feed themselves. Therefore, nowadays the concept according to which the development of cancer is angiogenesis dependent is generally recognized. This concept makes the control of tumoral angiogenesis one of the promising therapeutic ways in cancerology. The transition from the latent phase to the invasive and metastatic phase of a cancer is linked to what is called the angiogenic switch. It implies complex cellular and molecular interactions between cancerous cells, endothelial cells and the components of the extra-cellular matrix and namely the existence of specific proteins secreted by the tumoral cells able to stimulate the proliferation of capillary endothelial cells. Among them, VEGF, Vascular Endothelial Growth Factor was found in several types of tumors. It has shown a tumoral angiogenic activity in vitro and in vivo, and thus is a privileged target for the control of angiogenesis in an anti-tumoral goal. The role of VEGF in tumoral angiogenesis has been extensively studied. It has been proved to undergo as well autocrine as paracrine stimulation of tumoral angiogenesis. During the last few years, several members of the VEGF family have been described namely the VEGF-A, B, C, D, E and placenta growth factor (PlGF) among which VEGF-A (121 aminoacids) plays a role of prime importance in angiogenesis. VEGF is a 45 kDA glycoprotein, homodimeric, basic, and able to bind heparin. The three-dimensional structure of VEGF has been recently determined, by X-rays diffraction, and NMR spectroscopy. The different forms of the VEGF bind to receptors that exhibit a tyrosine-kinase activity (RTK). The specific action of the VEGF on the endothelial cells is mainly regulated by two types of RTK of the VEGF family, VEGFR1, or Flt-1, and VEGFR2, or KDR/Flk-1. Mutagenesis studies have shown that only a small number of VEGF residues are important and essential for the binding with RTK. Data described to date from the studies of VEGF/RTK interactions agree to the hypothesis that KDR receptor is the main human receptor responsible for the VEGF activity in both physiological and pathological vascular development, and VEGF-KDR signalling pathway has been validated as a priority target for the development of anti- and pro- angiogenic agents. Therefore angiogenesis mediated by VEGF constitutes a new target for anti-cancer therapy which has explored through different ways of intervention aiming at the blocking of the tumoral angiogenesis. The main ones are: -Struggle against the stroma degradation and invasion by the neo-vessels -Inhibition of activated endothelial cells. -Inhibition of angiogenic factors production and of their receptors. -Inhibition of the VEGF signal pathway, by peptides blocking the bond between VEGF and its receptors through the inhibition of intracellular transduction of VEGF signal. In conclusion, this bibliographic study allows to situate works of medicinal chemistry in the context of present knowledge concerning the vascular endothelial growth factor (VEGF) and its role in angiogenesis.

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